REMARKS

The Rejections under 35 USC § 112, first paragraph

Claims 5-8 and 21 were rejected under 35 USC § 112, first paragraph, as allegedly not being enabled by the disclosure.

A disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. *In re Brana*, 51 F.3d 1560 (Fed. Cir. 03/30/1995)

The Examiner has given no reason for doubt of the objective truth of the statements in the application, which must be relied on for enabling support. The only relevant concern of the Patent Office under these circumstances should be over the truth of any such assertion. The first paragraph of Section 112 requires nothing more than objective enablement, how such a teaching is set forth, either by use of the illustrative examples or by broad terminology, is of no importance. *In re Marzocchi*, 169 U.S.P.Q. 367 (CCPA 1971).

Applicants respectfully submit that it is the initial burden of the PTO to establish a reason to doubt the truth of the statements presented in the specification concerning utility. See, e.g., *In re Marzocchi et al.*, 169 USPQ 367, 370 (CCPA 1971) ("...it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure....") In the instant case, the rational presented is that it is not unusual for the hopes and expectations of a scientist (based on in vitro data) to be unfulfilled. Furthermore, the Office Action makes the assumption that all previous attempts at such treatment by medical researchers have met with failure because the Examiner was unable to find references citing successes. See Office Action page 3, middle of the page. This does not, however, establish a reason to doubt the truth of the statements of utility in Applicants' specification.

Merely because it is asserted that a specific example of treating a disease is not presented in the specification, one of ordinary skill in the art would not doubt the truth of the statements concerning the treatability of such diseases. MPEP § 2164.02 states that

compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. The nature of the invention and the state of the prior art further demonstrate that Applicants' specification provides sufficient guidance to objectively enable one of ordinary skill in the art to make and use the claimed invention. The specification teaches diseases which are treatable by the claimed compounds. The specification further teaches on, for example, page 20, lines 4-19, that the compounds of the invention can generally be administered in analogy to other known commercially available peptides, for example, analogously to the compounds described in US-A-4,472,305. Even preferred doses are set forth in the specification.

With regards to the Examiner's assumption of past failures, see, e.g., *Gould v. Quigg*, 822 F.2d 1074, 3 USPQ 2d 1302 (Fed. Cir. 1987). As of Gould's filing date, no person had built a light amplifier or measured a population inversion in a gas discharge. The Court held that "the mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." See id. (internal citations omitted.)

In regards to the terms "pharmaceutical composition", the Office Action alleges that the term implies an assertion of therapeutic efficacy. It is respectfully submitted that this term does not render the claims non enabled for at least the reasons discussed above. The specification teaches, for example, production of a pharmaceutical preparation by bringing compounds of formula I and/or their physiologically acceptable salts into a dosage form together with at least one solid, liquid and/or semi-liquid excipient or auxiliary. See, e.g., page 18, lines 22-29. More detailed guidelines are presented on page 18, line 34 to page 19, line 29, which includes teachings on suitable excipients. Examples A-I on pages 25-27 exemplify the preparation of pharmaceutical compositions.

The invention that one skilled in the art must be enabled to make and use is that defined by the claims. A pharmaceutical composition is a composition comprising an active compound and a pharmaceutically acceptable excipient or auxiliary. The pharmaceutical composition claims are thus composition claims. If a compound is allowed and thus found enabled, a composition comprising said compound and a pharmaceutically acceptable carrier will also be enabled, as pharmaceutically acceptable carriers are well known in the art, and are even exemplified in the specification.

Thus, with respect to claims directed at a pharmaceutical composition a composition is claimed, therefore, a composition is what needs to be enabled. The composition claims are not limited to a specified use as a method claim may be. The pharmaceutical compositions may be used for any purpose, including, e.g., the in vitro aspects taught in the specification or in vivo ones and others.

The Federal Circuit has specifically held that a composition claim can not be read to embrace only certain uses because the composition claims would otherwise mutate into a method claim. See *Union Oil Co. of California v. Atlantic Richfield Co.*, 208 F.3d 989 (Fed. Cir. 2000), wherein the Federal Circuit stated that "the '393 patent claims compositions of matter. The scope of these composition claims cannot ... embrace only certain uses of that composition. Otherwise these composition claims would mutate into method claims. The district court correctly applied this principle, refusing to narrow the scope of the claimed compositions to specific uses." See *id.* Accordingly, composition claims should not be treated as if they were method claims. A composition therefore comprising an enabled compound and a conventional pharmaceutically acceptable excipient must also be found enabled.

In any event, the Office Action acknowledges that evidence is of record showing that the claimed compounds antagonize $\alpha_v\beta_3$ in vitro and, further, it is acknowledged that antagonists of $\alpha_v\beta_3$ are known to effectively inhibit angiogenesis in vivo. The Office Action provides no rationale to refute a reasonable correlation, as discussed in Cross v. Izukia (see below)..

Since no reasons or evidence why the compounds would not be useful have been put forth herein, it is submitted that the burden has not been shifted back to applicants, and that objective enablement is clearly present.

Despite this, the Office Action appears to suggest, through the citation of *Forman*, that it would require undue experimentation to determine if the compounds are useful as stated. First, this analysis should not even be reached, in the absence of the "reasons or evidence" required under *Marzocchi*. Second, as long as a skilled worker can make the compounds, he or she can routinely test them to determine their relative activity. This degree of effort is fully routine, being nothing more than that expended by skilled workers on a day-

to-day basis in the field. It is by well settled law that the test for enablement is not whether any experimentation is needed but whether or not that experimentation is undue. See, *In re Angstadt*, 190 USPQ 214, 219 (CCPA 1976). Even a considerable amount of experimentation is permissible if it is routine. See, e.g., *Ex parte Jackson,* 217 USPQ 804, 807 (POBA 1982). Even if the experimentation needed is complex that does not necessarily make the experimentation undue under the enablement requirement. See also, for example, *In re Wands*, 8 USPQ 2nd 1400, 1404 (Fed. Cir. 1988) ("Enablement is not precluded by the necessity for routine experimentation."). Thus, undue experimentation is not present in the current situation, since one of ordinary skill in the art can easily, in view of what is already known in the art and in view of the guidance in the present specification, test the compounds for their relative activity. Accordingly, it can be seen that the full scope of the uses recited in the claims is enabled by the specification.

The Examiner enumerated a list of reasons for lack of enablement that are not proper for an enablement rejection under 35 USC § 112, first paragraph. Some of the reasons enumerated more typically appear in cases addressing practical utility under 35 USC § 101, or an enablement rejection in conjunction with a practical utility rejection. A deficiency under 35 U.S.C. 101 can also create a deficiency under 35 U.S.C. 112, first paragraph. See *In re Brana*, 34 USPQ.2d 1436 (Fed. Cir. 1995), but the converse is not true. "Office personnel should not impose a 35 USC § 112, first paragraph, rejection grounded on a 'lack of utility' unless a 35 USC § 101 rejection is proper." See MPEP § 2107. The Examiner makes a section 112 rejection and provides reasons more consistent with a section 101 rejection. Since there is no section 101 rejection, these reasons are irrelevant. Nevertheless they are discussed below.

The Office Action alleged that "it is not unusual for the hopes and expectations of a scientist (based on in vitro data) to be unfulfilled," and that "the reality is that all areas of pharmacology are unpredictable," and that "receptor antagonism, bioavailability and phamacokinetics are all 'unpredicatable.'" Opposite to these allegations, the Federal Circuit is of contrary opinion in analogous cases.

The Federal Circuit in *Cross v. Iizuka*, 753 F.2d 1040 (Fed. Cir. 1985), stated that in vitro results with respect to the particular pharmacological activity are generally predictive of in vivo tests results, i.e., when there is a reasonable correlation there between. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. Successful in vitro

testing for a particular pharmacological activity establishes a significant probability that in vivo testing for this particular pharmacological activity will be successful. A rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. *See Cross*, internal citations omitted. That is exactly the situation in the current case. Applicants demonstrated in vitro activity, for example by the Declaration submitted on July 30, 2002, in the specification by reference to P.C. Brooks, R.A. Clark and D.A. Cheresh in Science vol. 264, 569-71 (1994) on page 2, line 37 to page 4, line 8 (discussed in detail later).

The standards for a disclosure of practical utility and enablement laid down in *Cross* have been numerously reaffirmed and made stronger by later decisions. *See Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 08/28/1996), and *In re Brana*, 51 F.3d 1560 (Fed. Cir. 03/30/1995). In *Brana*, the court stated that in vivo tumor models represent a specific disease against which the claimed compounds are alleged to be effective. The court also stated that it is its firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment in humans. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful can be well before it is ready to be administered to humans. If the courts were to require Phase II testing in order to prove utility for pharmaceutical inventions, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer. *See Brana*, internal citations omitted.

The Federal Circuit in *Fujikawa v. Watanasin*, stated that "All that is required is the test to be reasonably indicative of the desired pharmacological response. ... There must be a sufficient correlation between the tests and the asserted pharmacological activity so as to convince those skilled in the art, to a reasonable probability, that the novel compound will exhibit the asserted pharmacological behavior." See *Fujikawa v. Watanasin*, 39 USPQ.2d 1895 (1996).

In *In re Bundy*, 209 USPQ 48, (1981), the disclosure did not have specific examples of the compounds claimed, and provided no example of specific use of any of the disclosed compounds. All that was established at the time of filing was the basic pharmacology for the

compounds. The specification stated that the compounds of the invention possess activity similar to E-type prostaglandins. Nevertheless it was found that sufficient guidelines as to use were given in the disclosure. The court held that "what is necessary to satisfy the how-to-use requirement of section 112 is the disclosure of some activity coupled with knowledge as to the use of this activity." *Id.*

Applicants satisfy these requirements. Applicants disclose that it has been found that the compounds of the formula I and their salts have very valuable pharmacological properties. In particular, they act as integrin inhibitors, and they inhibit in particular the interactions of the α_V, β_3 or β_5 integrin receptors with ligands, such as, for example, the binding of fibrinogen to the β_3 integrin receptor. The compounds show particular activity in the case of integrins $\alpha_V\beta_3$, $\alpha_V\beta_5$, $\alpha_{IIb}\beta_3$ and $\alpha_V\beta_1$, $\alpha_V\beta_6$ and $\alpha_V\beta_8$. See specification on page 2, lines 24-33. Applicants further teach that the compounds of formula I can be employed as pharmaceutically active substances in human and veterinary medicine, in particular for the prophylaxis and or therapy of diseases of the circulation, thrombosis, myocardial infarct, arteriosclerosis, inflammations, etc. See specification on page 3, line 29 to page 4, line 6. Applicants further teach other uses for the compounds, for example, such as their employment as antimicrobially active substances, as diagnostic aids in vascular systems in vivo, and as effective aids for studying the metabolism of blood platelets, etc. See page 4, line 7-30. All of these disclosures apply straightforward to the composition claims at issue.

The specification on page 2, line 37 to page 3, line 8, for example, teaches that the dependence of the beginning of angiogenesis on the interaction between vascular integrins and extracellular matrix proteins is described by P.C. Brooks, R.A. Clark and D.A. Cheresh in Science vol. 264, 569-71 (1994), *Brooks* hereinafter. Brooks teaches that angiogenesis plays a key role in development, wound repair, and inflammation. This process also contributes to pathological conditions such as diabetic retinopathy, rheumatoid arthritis, and cancer. See Brooks, page 569. Brooks investigated the expression of $\alpha_V\beta_3$ during angiogenesis, with human wound granulation tissue and chick tissue. The findings indicate that both human and chick blood vessels involved in angiogenesis have enhanced expression of $\alpha_V\beta_3$. Consistent with this result, expression of $\alpha_V\beta_3$ on cultured endothelial cells can be induced by various cytokines in vitro. (Brooks cites 3 different references) See Brooks, page 570. Further experiments on bFGF, TNF-α, and tumor cells demonstrated that $\alpha_V\beta_3$ plays a role in embryonic neovascularization and

that $\alpha_v\beta_3$ inhibits angiogenesis by directly affecting blood vessels rather than the tumor cells. See Brooks, page 570-71. Brooks concludes that the results demonstrate that integrin $\alpha_v\beta_3$ plays a key role in angiogenesis induced by a variety of stimuli. Brooks further teaches that "recent clinical trials have revealed that a function-blocking antibody directed to the β_3 subunit, reactive with $\alpha_v\beta_3$ as well as platelet $\alpha_{IIb}\beta_3$, significantly reduced symptoms of restenosis in patients who had undergone angioplasty." Brooks cites a reference in support. Brooks further concludes that together, these data suggest that integrin $\alpha_v\beta_3$ will be a useful therapeutic target for diseases characterized by neovascularization. See Brooks, page 571. Not only does the reference establish a correlation between $\alpha_v\beta_3$ and in vitro data, but actually establishes a correlation between $\alpha_v\beta_3$ and reduced symptoms of restenosis in patients undergoing clinical trials.

Again, the only relevant concern of the Patent Office at this point should be over the truth of assertions relating to enablement. The PTO must have adequate support for its challenge to the credibility of applicant's statements of utility. See *In re Marzocchi, supra.* The PTO did not provide support, i.e., reasons or evidence, to refute the asserted utility. The burden has never shifted to applicants to demonstrate utility.

The Examiner even admits in the Office Action that it is well known in the art that antagonist of $\alpha_v\beta_3$ are effective to inhibit angiogenesis in vivo, and that it is effective to inhibit apostosis. The Examiner proposes that applicants limit the claims to the noted uses.

The Examiner's allegation that "two compounds which are equally effective at antagonizing a receptor in vitro can exhibit very different efficacies in vivo" is untenable. The MPEP § 2164.02 directs an examiner to provide reasons for the conclusion that a correlation between in vivo and in vitro data is lacking. "Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an in vitro or in vivo animal model example." See MPEP § 2164.02. The Examiner made a conclusion without supporting evidence or an explanation of reasons why he/she doubts the correlation between in vivo and in vitro data. Brooks, supra, actually establishes a correlation between $\alpha_v\beta_3$ related in vitro activity and reduced symptoms of restenosis in patients undergoing clinical trials. The Examiner provided no support, reasons or evidence, to challenge the truth of the asserted correlation or correlations.

The Office Action also cites Dechantsreiter, J. Med. Chem., 42, 3033 (1999), and Haubner, J. Am. Chem. Soc., 118, 7881 (1996), to support the allegation that data from Haubner

is presented on the propensity of peptides to inhibit the binding between the $\alpha_v\beta_3$-integrin receptor and a ligand, that minor changes in structure can lead to a reduction in efficacy of more than 1000-fold, that the reality is that all areas of pharmacology are unpredictable, that the extent of binding of RGD peptides to cognate ligands is unpredictable, and that one can not predict, a priori, which result will be obtained, merely by viewing a structure.

Both of the cited documents teach structurally different compounds from the current invention. These references are thus irrelevant. Applicants nonetheless address the allegations based on the cited references.

First, the allegation that data is presented on the propensity of peptides to inhibit the binding between the $\alpha_v\beta_3$-integrin receptor and a ligand, is without basis. Haubner investigated the relationship between structure and bioactive conformation. See page 7882 , both columns. Haubner decreased the flexibility of peptide analogues by incorporating rigid building blocs. See page 7888-7889 and abstract. The fitting abilities are determined by the decreasing flexibility. See page 7890. Haubner in the abstract teaches that the incorporation of rigid turn motifs could not reduce the flexibility of the RGD site or fix a conformation which is unable to match a receptor very well. Thus, even when rigid building blocks were incorporated, binding occurred. The allegation that peptides have the propensity to inhibit binding is without basis. Further, the compounds according to the invention do not even contain rigid building blocks that would reduce its ability to fit a receptor geometry. Second, the allegation that minor changes in structure can lead to a reduction in efficacy of more than 1000-fold has no bearing on whether a given compound will have pharmaceutical value.

Third, the Office Action appears to hold the position that no patents should be granted for pharmaceuticals absent an in vivo demonstration of treatment of a given disease. However, the law is contrary to such a position, see, for example, *Cross*, supra. Fourth, the allegation that the extent of binding of RGD peptides to cognate ligands is unpredictable is also without basis. Haubner as discussed above teaches that even the incorporation of rigid building blocks could not reduce the flexibility of the RGD site or fix a conformation which is unable to match the receptor very well. See abstract. The specification on page 2, lines 24-33 teaches that the compounds of the invention were found to act as integrin inhibitors, in particular inhibiting the interactions of ... integrin receptors with ligands. The compounds show particular activity in the case of integrins ... $\alpha_v\beta_3$ .... The Office Action did not provide evidence or reason in support of doubt

regarding the truth of these assertions. Firth, the allegation that one can not predict, a priori, which result will be obtained, merely by viewing a structure has no bearing on the claimed invention. While neither reference teaches that one can predict the results by viewing a structure, both of the references investigate structure -activity relationships, see Dechantsreiter abstract, last line, and Haubner in the abstract as discussed above.

Claims 4 and 24-25 were rejected under 35 USC § 112, first paragraph, as allegedly is not enabled by the specification.

The Office Action alleges that the applicants do not reasonably convey that they had possession of the claimed invention because the compound prepared is never isolated. Applicants respectfully traverse these rejections. One of skill in the art can isolate a compound from a product mixture without the use of inventive skill. Isolation techniques are numerous and well known in the art. What is within the skill of one in the art need not be taught by a patent application, nor is an applicant obligated to recite every process step in a process claim.

Claim 4 is an open process claim meaning it uses the term comprising. Thus, claim 4 is open to the step of isolating the desired compound. Further, as the compounds prepared by the claimed process are novel, a reaction product mixture containing a novel compound is also novel. The reaction product mixture is useful as a material for providing the novel compound.

Claims 24 and 25 are also rejected because the Examiner could not find support for various derivatives. The specification on page 8, lines 1-8, discloses that the amino acids and amino acid residues mentioned can also be derivatized, the N-methyl, N-ethyl, N-propyl, N-benzyl or C-methyl derivatives are preferred. Additionally preferred are the methyl, ethyl, propyl, butyl, tert-butyl, neopentyl or benzyl esters of the side chain carboxyl group. Since Gly and Ala are amino acids according to the invention, see for example, the list of abbreviations on pages 4 and 5, there is sufficient disclosure for the derivatives of Gly or Ala. In any event, claims 24 and 25 are amended with regards to the described derivatives.

The Rejections under 35 USC § 112, first paragraph

Claims 1, 2, 4-8 and 11-31 were rejected under 35 USC § 112, second paragraph, as allegedly indefinite.

Claim 2 is amended. Support for the amendment can be found, for example, on page 6, lines 1-5, on page 21, lines 16-19, and page 9, lines 11-14.

Claim 4 as suggested by the Examiner is split up into several claims to enhance its clarity. Claims 4, and 32-34 are directed to the subject matter of claim 4 prior to the amendment.

The Office Action alleges that claim 4 is indefinite as to the process steps because it fails to recite an isolation step for the final product. A section 112, first paragraph, rejection was also issued for the same reason. The arguments from above are incorporated herein. The Office Action states "If a person walks into a bank, is it the case that the person automatically acquires possession of the money that is present in the vault? As with the chemist, at least one additional step is necessary to achieve the objective." Applicants are puzzled by the analogy, but do understand that if an isolated product is desired, an isolation step is necessary. Such an isolation step, however, need not be taught by the specification as isolation steps are well known in the art. The language of the claim makes it clear that an isolation step is not precluded. Furthermore, the process claimed provides the desired novel product, regardless of whether the product is isolated or is present as a component of a mixture. The process is thus clearly useful.

With respect to the terms reactive derivative and functional derivative, one of skill in the art can readily ascertain the scope of these terms. These terms are widely used in the art and the specification gives examples of each to define the scope of the terms on page 13 line 31 to page 15, line 2.

The carbonyl oxygen atom and the hydroxyl group are placed back on the first of the Z substituents. Support can be found, for example, in original claim 4. The missing groups are a result of an obvious typographical error. No new matter is added.

Claim 5 is amended to further clarify the claim. No change in scope is achieved.

Claim 6 is amended to further clarify the claim. One of skill in the art understands the meaning of excipient, and thus would understand what at least one excipient means too. The specification also defines the term and offers specific examples of excipients on page 18, line 34 to page 19, line 20. The term "sustained administration" is also a term that has a recognized meaning in the art and thus one of skill in the art would understand its scope and meaning.

The typographical error in claim 7 is corrected. The Office Action alleges that the claim is indefinite with regard to which "diseases of the circulation" and which "coronary heart diseases" are intended. One of skill in the art readily understands the scope and meaning of each of these terms. The Office Action does not allege that there is a disagreement among skilled artisans regarding the scope of these terms. The breath of the term is irrelevant to whether it is definite or not. The Office Action also alleges that the process is indefinite with respect to the process steps and endpoint. Applicants respectfully disagree. The term "a patient in need thereof" defines the condition and the patient to be treated. The Office Action also alleges that a tumor is not a disease but a manifestation of a disease. A patentee can be his own lexicographer, and applicants define tumor as a disease. Additionally Webster's Third New International Dictionary, Unabridged, defines disease as "an impairment of the normal state of the living animal." Relevant page of reference is attached. A tumor is an impairment of the normal state of a living animal. Thus, applicants' definition of a tumor as a disease is not contrary to the accepted definition of a disease, and is thus proper.

Regarding claim 8, one of skill in the art readily understands what is meant by a pathological process that is supported or propagated by angiogenesis. The question of determining how far "upstream" or "downstream" can one go in deciding whether the process is supported or propagated by agiogenesis is irrelevant. The method is equally applicable to both as claimed. Furthermore, an applicant does not have to teach in a patent application and/or claim through its claims what is already known by those of skill in the art.

Regarding claims 1 and 20, the derivatives of the amino acid according to the invention are defined by the specification on page 8 lines 1-8.

Claim 22 is amended to depend from claim 4.

Claims 23-25 are amended to clarify the claims. Claims 24 and 25 are also corrected with regard to the derivatives claimed as discussed previously. No change in scope is achieved.

Request Regarding Withdrawal of Office Action's Finality

Applicants respectfully request the finality of the Office Action to be withdrawn. The Office Action makes numerous new grounds of rejections which were not necessitated by the amendments filed in response to the previous Office Action. New grounds of rejections are made, for example, with respect to claim 4, i.e., the indefiniteness rejection regarding the claim's

failure to recite that the reaction is carried out for a time and under conditions effective to achieve the intended results, the indefiniteness rejections for the recitation of cyclizing agent, functional derivative and reactive derivative, and the indefiniteness rejection regarding the alleged inconsistency of the claimed compound and the salt formed in part (c); and all indefiniteness rejections over claims 5, 6 and 7. In light of the foregoing, the withdrawal of the Office Action's finality is requested.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version With Markings To Show Changes Made**".

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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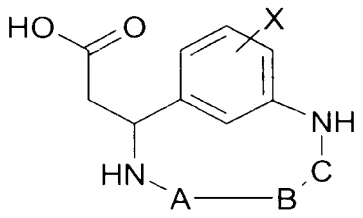
Version With Markings To Show Changes Made

In the Claims

The claims have been amended as follows:

1. (Amended) A compound of the formula I

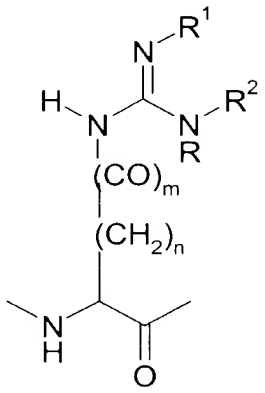


I

in which

A is Gly, Ala, derivatized Gly, derivatized Ala or NH-NH-CO,

B is a radical of the formula II



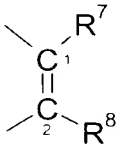
C is $-(CO)_p-(CH_2)_q-(CO)_r-$ or $-(CO)_p-CH=CH-(CO)_r-$,

m, p, r are in each case independently of one another 0 or 1,

n, q are in each case independently of one another 1, 2, 3, or 4,

R^1 and R^2 are independently of one another H or alkyl, or

R^1 and R^2 ~~can~~ are together ~~be~~



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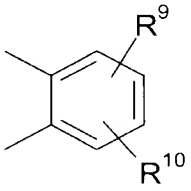


R^7, R^8, R^9, and R^{10} are each, independently of one another, H, alkyl, Ar, OR^6, Hal, NO_2, $NR^6R^{6'}$, $NHCOR^6$, CN, $NHSO_2R^6$, $COOR^6$ or COR^6,

X is H, Hal, alkyl or Ar,

Ar is phenyl which is unsubstituted or mono-, di- or trisubstituted by R^3, R^4 or R^5 or is unsubstituted naphthyl,

R^3, R^4, R^5 are each, independently of one another, R^6, OR^6, Hal, NO_2, $NR^6R^{6'}$, $NHCOR^6$, CN, $NHSO_2R^6$, $COOR^6$ or COR^6,

R^6, $R^{6'}$ are each, independently of one another, H, alkyl, phenyl or benzyl, and

Hal is F, Cl, Br or I,

wherein each optically active amino acid or its derivative is of the D or L configuration; ~~acids or derivatives thereof can be in either their D or L forms; and~~

or a physiologically acceptable ~~salts~~ salt thereof.

2. (Amended) A compound according to claim 1, wherein said compound is in the form of a single stereoisomer ~~enantiomer or single diastereomer~~.

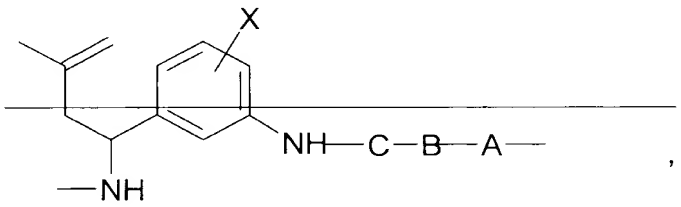
4. (Amended) A process for ~~the preparation of~~ preparing a compound according to Claim 1 comprising

~~(a)~~ treating with ~~a cyclizing agent~~ an agent suitable to achieve cyclisation a compound of ~~the~~ formula III

H-Z-OH III

in which

Z is



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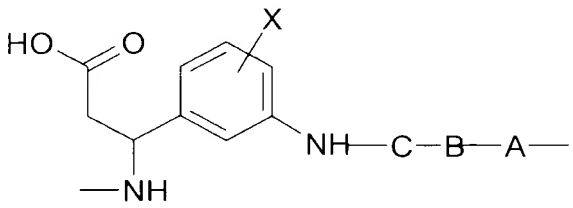

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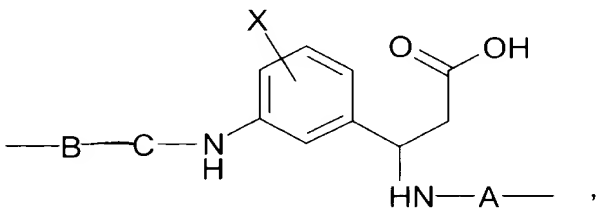
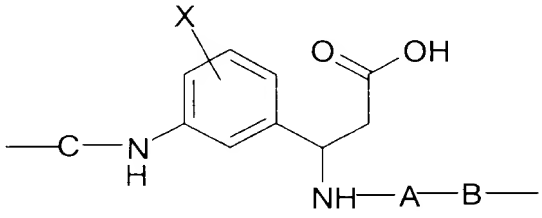
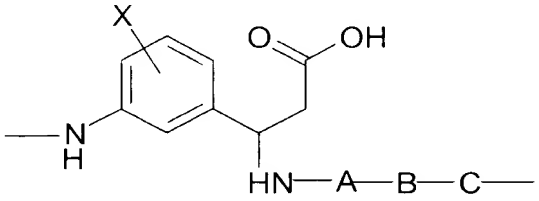




or



and X, A, B and C have the meanings indicated in Claim 1~~, or a reactive derivative of a compound of the formula III, to obtain a compound according to claim 1, or~~

~~b) treating a functional derivative of a compound of the formula I with a solvolysing or hydrogenolysing agent, to obtain a compound according to claim 1, and/or~~

~~c) converting a basic of acidic compound of the formula I into one of its salts by treatment with an acid or base~~ for a time and under conditions effective to obtain a compound according to claim 1.

5. (Amended) A process for ~~the production of~~ preparing a pharmaceutical ~~preparation~~ composition that contains a compound according to Claim 1 comprising bringing

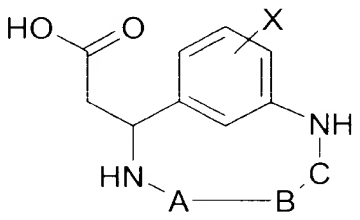
said ~~a~~ compound according to Claim 1 into a ~~suitable~~ dose form together with ~~a~~ at least one solid, liquid or semi-liquid excipient or auxiliary.

6. (Amended) A pharmaceutical composition comprising at least one compound according to Claim 1, and at least one excipient suitable for sustained administration, parenteral administration, topical application, or administration by inhalation spray.

7. (Amended) A method for the treatment of diseases of the circulation, thromboses, cardiac infarct, coronary heart diseases, arteriosclerosis, apoplexy, angina pectoris, tumours, osteoporosis, inflammations, infections or ~~resenosis~~ restenosis after angioplasty, comprising administering to a patient in need thereof an integrin inhibitory effective amount of a compound according to claim 1.

8. (Amended) A method for treating a pathological process that is ~~the treatment of pathological processes which are~~ supported or propagated by angiogenesis, comprising administering to a patient in need thereof of an effective amount of a compound according to claim 1.

20. (Amended) A compound of ~~the~~ formula I

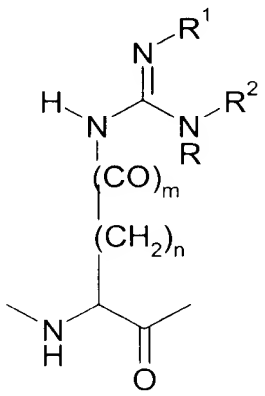


I

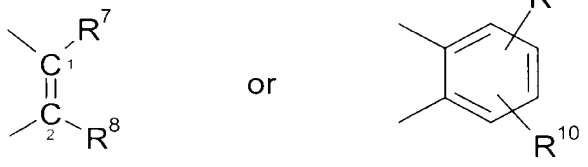
in which

A is Gly, Ala, derivatized Gly, derivatized Ala or NH-NH-CO,

B is a radical of the formula II



C	is $-(CO)_p-(CH_2)_q-(CO)_r-$ or $-(CO)_p-CH=CH-(CO)_r-$,
m, p, r	are in each case independently of one another 0 or 1,
n, q	are in each case independently of one another 1, 2, 3, or 4,
R^1 and R^2	are independently of one another H or alkyl, or
R^1 and R^2	~~can~~ are together ~~be~~



R^7, R^8, R^9, and R^{10}	are each, independently of one another, H, alkyl, Ar, OR^6, Hal, NO_2, $NR^6R^{6'}$, $NHCOR^6$, CN, $NHSO_2R^6$, $COOR^6$ or COR^6,
X	is H, Hal, alkyl or Ar,
Ar	is phenyl which is unsubstituted or mono-, di- or trisubstituted by R^3, R^4 or R^5 or is unsubstituted naphthyl,
R^3, R^4, R^5	are independently of one another R^6, OR^6, Hal, NO_2, $NR^6R^{6'}$, $NHCOR^6$, CN, $NHSO_2R^6$, $COOR^6$ or COR^6,
R^6, $R^{6'}$	are independently of one another H, alkyl, phenyl or benzyl, and

Hal is F, Cl, Br or I,

wherein each optically active amino acid or its derivative is of the D or L configuration; ~~acids or derivatives thereof can be in either their D or L forms; and salts~~

or a salt thereof.

22. (Amended) A process for the preparation of a compound according to claim ~~1~~ 4 comprising

(a) cyclizing a compound of formula III in the presence of ~~a cyclizing agent~~ an agent suitable to achieve cyclization for a time and under conditions effective to obtain a compound according to claim 1; and

(b) isolating the compound of claim 1.

23. (Amended) A compound according to Claim 1, which is:

a) (8S,14S)-2-(8-(3-guanidinopropyl)-3,6,9,12-tetraxoxo-2,7,10,13-tetraazabicyclo[13.3.1]nonadeca-16,18,19-trien-14-yl)acetic acid or a physiologically acceptable salt thereof;

b) (9S,15S)-2-(9-(3-guanidinopropyl)-3,7,10,13-tetraoxo-2,8,11,14-tetraazabicyclo[14.3.1]eicosan-17,19,20-trien-15-yl)acetic acid or a physiologically acceptable salt thereof;

c) (8S,14S)-(8-(3-guanidinopropyl)-18-methyl-3,6,9,12-tetraoxo-2,7,10,13-tetraazabicyclo[13.3.1]-nonadeca-1(18),15(19),16-trien-14-yl)acetic acid or a physiologically acceptable salt thereof; or

d) (6S,12S)-(6-(3-guanidinopropyl)-4,7,10-trioxo-2,5,8,11-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-trien-12-yl)acetic acid, or a physiologically acceptable salt thereof.

24. (Amended) A compound according to Claim 1, wherein A is Gly, Ala, derivatized Gly or derivatized Ala, and wherein derivatized Gly is selected from the group consisting of N-methyl, N-ethyl, N-propyl, and N-benzyl, ~~and C_α-methyl~~ derivatives ~~and the methyl, ethyl, propyl, butyl, tert-butyl, neopentyl, or benzyl esters of the side chain carboxyl group~~, and derivatized Ala is selected from the group consisting of N-methyl, N-ethyl, N-

propyl, N-benzyl, and C_α-methyl derivatives ~~and the methyl, ethyl, propyl, butyl, tert-butyl, neopentyl, or benzyl esters of the side chain carboxyl group~~.

25. (Amended) A compound according to Claim 20, wherein A is Gly, Ala, derivatized Gly or derivatized Ala, and wherein derivatized Gly is selected from the group consisting of N-methyl, N-ethyl, N-propyl, and N-benzyl, ~~and C_α-methyl~~ derivatives ~~and the methyl, ethyl, propyl, butyl, tert-butyl, neopentyl, or benzyl esters of the side chain carboxyl group~~, and derivatized Ala is selected from the group consisting of N-methyl, N-ethyl, N-propyl, N-benzyl, and C_α-methyl derivatives ~~and the methyl, ethyl, propyl, butyl, tert-butyl, neopentyl, or benzyl esters of the side chain carboxyl group~~.

Claims 32-34 have been newly added.